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Tattoo Reactions Associated with Targeted Therapies and Immune Checkpoint Inhibitors for Advanced Cancers: A Brief Review

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Keywords

Immune checkpoint inhibitor · Granuloma ·
Molecular targeted therapies · Sarcoidosis · Tattooing

Introduction

Cutaneous reactions on permanent tattoos have been reported in the past during immune restoration syndrome under highly active antiretroviral therapy for human immunodeficiency virus [1, 2] as well as during interferon therapy for hepatitis C with the induction of sarcoidosis [3, 4]. Besides, anecdotal cases of granulomatous tattoo reaction under tumor necrosis factor α inhibitors have been reported [5]. Inhibitors of the mitogen-activated protein (MAP) kinase pathway and immune checkpoint inhibitors (ICPIs) are widely used now in the management of advanced malignancies. However, ICPIs are associated with a wide range of dermatologic manifestations including sarcoidosis [6] and granulomatous reactions [7]. With the increased popularity of tattoos worldwide, cases of tattoo reactions are slowly increasing. We reviewed here all the case reports of tattoo reactions associated with targeted therapies and ICPIs.

Materials and Methods

We performed a review of the existing English- and French-language literature on patients who developed a reaction on ≥ 1 tattoo during or after targeted therapies and ICPIs. The databases MEDLINE (1946–2019) and Scopus (1823–2019) were initially searched on June 6, 2019. The following keywords were used: tattoo, tattoos, tattooing, molecular targeted therapies, BRAF inhibitor; MEK inhibitor; immune checkpoint inhibitor; as well as the following molecules: avelumab, nivolumab, pembrolizumab; ipilimumab; dabrafenib, encorafenib, vemurafenib; binimetinib, cobimetinib, trametinib. All the articles reporting on ≥ 1 case(s) of targeted therapies/ICPI-associated tattoo reactions were included. We also included conference abstracts if relevant.

Results

To the best of our knowledge, 10 cases (6 men, 4 women; mean age 44.5 years, range 22–59) have been reported since 2012. The main characteristics are summarized in Table 1. Six patients received a combination of BRAF inhibitor (BRAFi) associated with a MEK inhibitor (MEKi), 2 patients a PD-1/PD-L1 inhibitor (PD-1i/PD-L1i) and 2 patients a CTLA-4 inhibitor (CTLA-4i), including one in combination with a PD-1i. We found that the clinical presentation was different according to culprit drugs. Tattoo eruption associated with BRAFi + MEKi presented mostly as a complete infiltration/induration of dark-colored tattoos with striking inflammatory borders in 5 out of 6 cases [10–13, 16]. Tattoo reactions with CTLA-4i or PD-1i/PD-L1i were reminiscent of what is usually observed with sarcoidosis or granulomatous tattoo reactions in general, e.g. papules and nodules scattered within black tattoos [8, 9, 14, 15]. Tattoos were dark/black in 86% (6/7) of the cases. In case of multicolored tattoos, other colors were spared. Delays of onset after the first cycle were as follows from the earliest to the latest: CTLA-4i + PD-1i (2 months) > BRAFi + MEKi (2–6 months) > PD-1i/PD-L1i (9–15 months). Only 1 patient had additional cutaneous sarcoids on plain skin and erythema nodosum [9]. Biopsies showed noncaseating granulomas in 67% (6/9), including all the cases with CTLA-4i and/or PD-1i/PD-L1i. In the 3 remaining cases, there was only a lymphocytic infiltration without any granulomas [10, 12, 13]. Angiotensin-converting enzyme was elevated in 2 cases of granulomatous reactions [9, 15]. Lung involvement and lymph nodes were reported in 60% (6/10). Management was highly variable according to authors. It included local corticosteroids, combination of local and systemic corticosteroids, abstention with either maintenance or discontinuation of the treatment, and switch to PD-1i or surgery. One patient experienced relapses with BRAFi + MEKi cycles [10]. Overall, outcome was always favorable.

Discussion

Granulomatous eruptions under ICPIs are an uncommon immune-related adverse event that can become more and more frequently encountered with the increased use of this therapeutic class [7]. All the patients under PD-1i/PD-L1i/CTLA-4i developed sarcoid-like reactions on tattoos. Delays of onset and outcomes were here in line with what is known from the literature [7]. On the other hand, cutaneous granulomatous reactions and sarcoidosis are rather infrequent with BRAFi [17]. Out of the 5 patients under BRAFi + MEKi with available biopsies, 3 displayed a lymphocytic infiltration in the dermis without granulomas. Besides, the clinical presentation was rather different with a marked erythema around the tattoos which is totally unusual compared to the usual tattoo granulomatous reactions we often see in practice [4, 18, 19]. Only 1 patient did not present such an inflammatory reaction around the affected tattoos [16]. To date, there is no case report of tattoo reaction with BRAFi alone. In 1 patient [11], the reaction developed 3 months after MEKi introduction. The differ-

Table 1. Review of 10 cases of patients with tattoo reaction with targeted therapies or immune checkpoint inhibitors for advanced cancer

| Gender/ age, years | Cancer | Metastases | Therapy | Tattoo | Symptoms | Affected color | Pathology | Delay | ACE | Other symptoms | Outcome | Ref. |
|--------------------------|------------------|----------------------------|-------------------|--|---|-------------------|---|--|-----|---|---|------|
| F/47 | Melanoma | LN | CTLA-4i | PMU | Yellowish papules, nodules and infiltration of the eyebrows | NA | Noncaseating multinucleated giant cell granulomas | 9 months | N | Mediastinal LN and lung micronodules | Spontaneous regression in 9 months | 8 |
| M/52 | Urothelial Ca | NA | CTLA-4i+ PD-1i | Tattoos (n = 2) | Papules and thickening | Black | Sarcoidosis (biopsy from a sarcoid, not from the tattoo reaction) | 2 months | ↑ | Skin sarcoids, hilar LN; joint tenderness; erythema nodosum | Efficacy of sCS + treatment disruption | 9 |
| F/42 | Melanoma | Lung | BRAF + MEKi | 10-year-old tattoos | Inflamed and indurated tattoos | Black | CD4 > CD8 lymphocytic infil- trate, no granuloma | 6 months | NA | – | Relapses with BRAFi + MEKi efficacy of sCS and ICS | 10 |
| M/54 | Melanoma | NA | BRAF + MEKi | All tattoos | Inflammation and infiltration of all the tattoos | NA | NA | 2 years (BRAF), 3 months (MEKi) | N | LN | Stability, treatment main- tained | 11 |
| F/42 | Melanoma | NA | BRAF + MEKi | All tattoos | Inflammation and infiltration of all the tattoos | NA | Lymphocytic infiltration and noncaseating epithelioid granu- loma | 3 months | NA | LN, dry cough | Efficacy of short course of sCS; no relapse, treat- ment maintained | 11 |
| M/58 | Melanoma | NA | BRAF + MEKi | 20-year-old tattoos (n = 3) | Inflammation and infiltration of all the tattoos | Black | Lymphohistiocytic infiltration without granuloma | 2 months | N | – | Regression within 15 days after treatment withdrawal | 12 |
| F/34 | Melanoma | Lung | BRAF + MEKi | 18-year-old tattoo (n = 2), other spared | Papules, burning, tenderness, swelling | Dark | Lymphocytic infiltrate, no granuloma | 6 months | NA | LN involvement | Switch to pembrolizumab, without relapse | 13 |
| M/22 | HL | – | PD-1i | 1 tattoo | Erythematous partly eroded plaque | Red | Pseudoepitheliomatous hyper- plasia, eosinophils, plasma cells, lymphoid elements, noncaseat- ing granulomas | 9 months | NA | – | Surgery, treatment with- drawal | 14 |
| M/59 | Lung Ca | Adrenal and cerebral | PD-L1i | 40-year-old tattoo | Infiltrated papules | Black | Noncaseating epithelioid and multinucleated giant cell granu- lomas | 15 months | ↑ | Mediastinal LN | Efficacy of ICS within a few days | 15 |
| M/30 | Melanoma | Lung, mediasti- num, LN | BRAF + MEKi | NA, several tattoos | Slightly itchy, infiltrat- ed papules | Black | Histiocytic infiltrate and noncaseating granulomas | 4 months | N | – | Partial improvement of itch with ICS | 16 |

ACE, angiotensin-converting enzyme; BRAFi, BRAF inhibitor; Ca, carcinoma; CTLA-4i, CTLA-4 inhibitor; F, female; HL, Hodgkin lymphoma; L, lung; LN, lymph node; ICS, local corticosteroids; M, male; MEKi, MEK inhibitor; N, normal; NA, not available; PMU, permanent make-up tattoo; sCS, systemic/oral corticosteroid.

ences observed in histology may be related to sampling, and repeated biopsies could disclose genuine granulomas. Another hypothesis is that those reactions belong to different parts of the same spectrum of cutaneous immune-related adverse events.

The physiopathogeny of granuloma formation under ICPIs may be related to the activation of the innate immune system, the dysfunction of regulatory T cells and the expansion of Th7 cells. Reduction of CTLA-4 expression may contribute to increased proliferation capacity [7]. On the other side, the inhibition of BRAF and MEK could lead to a paradoxical activation of ERK as reported recently [20]. Besides, the inhibition of MEK, which is a negative regulator of AKT [21], could lead to a possible activation of the AKT/mTOR pathway, which could induce the formation of granulomas [22]. This review is limited by the low number of cases and the quality of the reports, sometimes originating from posters.

With the increased prevalence of tattoos among the population, tattoo reactions associated with targeted therapies and immunotherapies for cancer may become more frequent. Those reactions affect mostly old black tattoos. We cannot rule out that the seeming affinity of those reactions to black tattoos is fortuitous. Histologically reactions range from lymphocytic infiltration to granulomatous reaction. They may be associated with genuine systemic sarcoidosis that should not be mistaken for metastatic progression [7]. Close monitoring is mandatory, invasive biopsies may be necessary if in doubt. Outcome is usually favorable, and treatment discontinuation is not obligatory.

Key Message

The use of immune checkpoint inhibitors and targeted therapies for advanced cancers may lead to granulomatous reactions and sarcoidosis within tattoos.

Disclosure Statement

The authors declare no conflict of interest.

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